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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/494,212	LIN ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-18,20,22,23,25,26 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-18,20,22,23,25,26 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 7-18, 20, 22, 23, 25, 26 and 29-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

3. For convenience, claims 1 and 22, the only independent claims currently pending, are reproduced below.

Claim 1 (currently amended): A method of generating amplified messenger RNAs using polymerase ~~reaction activity~~ reactions, comprising the steps of:

(a) providing a plurality of intracellular messenger RNAs for following steps (b) to (e);

(b) contacting said messenger RNAs with a plurality of first oligodeoxythymidylate-containing primers to form a plurality of first-strand complementary DNAs, wherein said first-strand complementary DNAs are generated by reverse transcription of said messenger RNAs with extension of said first primers;

(c) permitting terminal extension of said first-strand complementary DNAs to form a plurality of polynucleotide-tailed first-strand complementary DNAs, wherein said polynucleotide-tailed first-strand complementary DNAs are tailed by multiple copies of deoxynucleotides;

(d) incubating denatured said polynucleotide-tailed first-strand complementary DNAs with a plurality of second primers to form a plurality of double-stranded complementary DNAs, wherein said double-stranded complementary DNAs are generated by extension of DNA polymerase activity with said second RNA promoter-linked primers; and

(e) permitting transcription of said double-stranded complementary DNAs to form a plurality of amplified sense-oriented full-length RNAs, wherein said amplified sense-oriented full-length RNAs are generated by extension of RNA polymerase activity through the RNA promoter region of said double-stranded complementary DNAs.

Claim 22 (currently amended). A method of performing improved messenger RNA amplification, comprising the steps of:

(a) providing a plurality of messenger RNAs for following steps (b) to (f);

(b) generating a plurality of ~~polynucleotide-ended~~ polynucleotide-tailed complementary DNAs from said messenger RNAs, wherein said ~~polynucleotide-ended~~ polynucleotide-tailed complementary DNAs are reverse-transcribed from said messenger RNAs and tailed by multiple deoxynucleotides in the ends;

(c) permitting denatured said polynucleotide-tailed complementary DNAs to form a plurality of double-stranded complementary DNAs, wherein said double-stranded complementary DNAs contain a complementary DNA sequence flanked with an RNA polymerase promoter and a polynucleotide-tail; and

(d) incubating said double-stranded complementary DNAs in a plurality of promoter- and tail-dependent extension systems, and thereby providing a plurality of amplified RNAs from said messenger RNAs.

4. For purposes of examination, the claimed methods have been interpreted as encompassing the generation of only full-length cDNAs and mRNAs, performing an infinite number of cycles of amplification, and the addition of DNA and RNA polymerases but a single time for any number of cycles of amplification.

5. Page 10, last paragraph, teaches that one must add RNA polymerase "in every round of transcription due to the denaturation step."

6. In view of the breadth of the claims, and the specific limitations taught in the specification, the specification has not been found to provide an adequate written description of the full scope of the claimed invention so as to reasonably suggest that applicant, at the time of filing, had possession of the now-claimed invention. Accordingly, claims 1-3, 7-18, 20, 22, 23,

25, 26 and 29-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

7. At page 8 of the response received 02 April 2004, hereinafter the response, applicant asserts that the specification has been misinterpreted with regard to the number of times that polymerase needs to be added to the reaction mixture, but admits that thermostable RNA polymerases are not yet available.

8. Applicant's arguments have been fully considered and have no been found persuasive towards the withdrawal of the rejection for the claimed method fairly encompasses performing an infinite number of cycles of amplification with but a single addition of polymerase, which is admittedly thermolabile. Applicant is urged to consider amending the claims to where but a single cycle of amplification is performed or amend the claims to where polymerase is added at each cycle. In the absence of such limitations of the claims or convincing evidence to the contrary, the rejection is maintained.

9. Claims 1-3, 7-18, 20, 22, 23, 25, 26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' "

> *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

10. For purposes of examination, the method of said claims has been interpreted as encompassing the production of mRNA of any length, where said mRNA has secondary structures, and where virtually any DNA or RNA polymerase can be used.

11. The specification has been found to set forth the following five examples.

a. Example 1, page 13: "Cell Fixation and Permeabilisation."

b. Example 2, pages 13-14: "First Reverse Transcription and Polynucleotide Tailing of the First-Strand cDNAs"

c. Example 3, page 14: "Denaturation, Double-stranded cDNA Synthesis and Transcriptional Amplification"

d. Example 4, page 15: "Second Reverse Transcription, Denaturation, Double-Stranded cDNA Synthesis and mRNA Amplification"

e. Example 5, page 16: "Amplification Cycling Procedure"

12. The above-cited example, however, do not teach the skilled artisan how to overcome art-recognized problems and difficulties.

13. The claimed method clearly requires the use of a RNA polymerase so to generate a plurality of full-length mRNA. However, the use of RNA polymerase is not without difficulties. US Patent Publication 2003/0087275 teaches:

> [0051] The TATA box or the like, which may be comprised in the DNA sequence for regulating transcription of the invention can be found in various species ranging from simple eukaryotes such as baker's yeast to more complex organisms such filamentous fungi and humans. The TATA box assists in directing RNA polymerase (RNA polymerase 11) to the downstream mRNA initiation site. The RNA polymerase binds to regions of DNA, i.e., the RNA polymerase [*sic*] binding site often in general referred to as a promoter. The TATA box is in most cases necessary for transcription because the RNA polymerase normally cannot recognize the initiation sites on its own. The TATA box directs the RNA polymerase to the m RNA initiation site once the RNA polymerase has bound to the TATA box. Yet another problem occurs when the RNA polymerase scans for the TATA box. The RNA polymerase cannot recognize the TATA box on its own. It has to use (a) transcription factor(s) to find the TATA box. After the transcription factor(s) bind(s) to the TATA box, then the RNA polymerase can recognize and bind to the TATA box. Then the RNA polymerase binds to the transcription factor(s), which identify the TATA box. The TATA box then guides the RNA polymerase to the mRNA initiation site where transcription can begin. (Emphasis added)

The claimed method does not require any TATA box to be present in the cDNA, or any transcription factors be used. As shown above, both are required in order for the RNA polymerase to bind to the appropriate site on the cDNA such that transcripts are produced.

14. US Patent Publication 2003/0040099 teaches:

> [0015] However, successful generation of highly infectious cDNA clones has often been problematic due to the presence of mutations in the virus RNA template population

> caused by the inherent mutability of RNA viruses, the relatively low fidelity of the DNA polymerases used in cDNA synthesis, instability and toxicity of viral sequences in bacterial hosts, and the infidelity of the RNA polymerases used for in vitro transcriptions. (Emphasis added)

The specification is essentially silent as to how one of skill in the art is to be overcome the issue of fidelity. Assuming *arguendo*, that only full-length amplicons are produced, the specification is silent as to how the skilled artisan would be able to recognize those amplicons that have an incorrect sequence over that of one, which is correct. Accordingly, one may well produce "full length" mRNA, yet the sequence no longer encodes the intended protein, or any protein, if a mutation, e.g., substitution, occurs early on in the sequence.

15. US Patent 6,303,306 B1 states:

> Amplification efficiency is high in the amplification system based on replicated RNA. However, because of a poor heat stability of conventional enzymes, namely RNA dependent DNA polymerase, DNA dependent RNA polymerase and DNA dependent DNA polymerase, the reaction temperature does not have to be high, and non-specific hybridization between the nucleic acid as a template and the primer cannot be avoidable, so that decrease of the specificity is a problem. In addition, the instability of the enzymes creates a severe problem in supplying and storing enzymes, and storage in a frozen state or in a refrigerator is required. (Emphasis added)

With non-specific hybridization taking place, one may well achieve priming of the incorrect sequence. Additionally, the incorrectly primed sequence as well as the correctly primed sequence can give rise to further erroneous amplicons/transcripts when one considers the aspect of infidelity of the polymerases, be they DNA or RNA.

16. The claimed method also is considered to encompass the incorporation of fluorescently labeled nucleotides. However, the art recognizes that such nucleotides cannot be incorporated in RNA produced via a DNA dependent RNA polymerase. In support of this position, attention is directed to US Patent 6,140,053, which states:

> Another problem, which still needs to be resolved, is that DNA/RNA polymerases, which are able to use the four fluorescently labeled NTPs instead of the unmodified counterparts, have not been identified.

17. Yet another problem confronting RT-PCR is when the mRNA contains secondary structures. In support of this position, attention is directed to US Patent Publication 2003/0180737, which states:

> RNA molecules with secondary structure may be poorly represented in cDNA libraries. Populations of RNA with secondary structure may also yield cDNA libraries with a short insert size. Furthermore, RNA molecules containing secondary structure may be difficult to detect in assays such as reverse transcription-polymerase chain reaction (RT-PCR). (Emphasis added)

18. Attention is also directed to column 40 of Jones (US Patent 5,858,671), which teaches at length of the problems associated with enzymatic coupling efficiency and accuracy of nucleotides. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant levels. For example, during oligonucleotide synthesis of a 70-mer, requiring 69 couplings, a 99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ($0.99^{69} = 0.50$)." In the present case, applicant is claiming a product that would be the result of an infinite number of couplings, not just 69 as described above.

19. While a disclosure is not required to teach each and every embodiment encompassed by the claims, the specification, "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the" invention. The record clearly indicates that the invention is drawn to an area of technology replete with art-recognized difficulties. The instant disclosure, however, is essentially silent as to

how one is to ensure that they obtain only full-length cDNA such that full-length mRNA is ultimately transcribed from the amplified cDNA population. The failure of the instant disclosure to fully enable the claimed invention unfairly and inappropriately shifts the burden of enablement from applicant to that of the public. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

Here, however, the level of enabling disclosure provided does not vary inversely with the degree of unpredictability of the factors involved. The shifting of the burden of enablement is unfair and level of experimentation required for he public to practice the full breadth of the claimed invention is undue. Accordingly, and in the absence of convincing evidence to the contrary, claims 1-3, 7-18, 20, 22, 23, 25, 26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement

Response to argument

At page 8, bridging to page 9 of the response applicant asserts that the specification enables skilled artisans to overcome art-recognized issues by performing certain critical steps. Such limitations, however, are not recited in the claims. Rather, the claims fairly encompass practicing the claimed invention where such art-recognized issues are to e expected. Applicant is urged to consider amending the claims such that they recite those limitations necessary to overcome these art-recognized difficulties.

20. At page 9 of the response, applicant asserts that the Office has engaged in unreasonable speculation as to problems or difficulties to be encountered. Applicant points to publications and a review of specific disclosures found in the body of the specification.

21. The above argument ahs been fully considered and has not been found persuasive towards the withdrawal of the rejection. While applicant has pointed to various published documents, such publications do not take the place of a sworn declaration. Further, while attention has been directed to certain specific embodiments di8sclosed within the specification, the claims are not so limited. Further, applicant has not presented convincing evidence that the claimed method do not fairly encompass those embodiments cited in the art that are recognized as being problematic. Therefore, and in the absence of convincing evidence to the contrary, he rejection is maintained.

22. At page 10 agreement is reached in that there is no perfect enzyme, yet assert that the reference of US patent Application Publication 2003/0040099 is "**NOT** appropriate" (emphasis in the original) as there are commercially available enzymes that exhibit high fidelity.

23. The above argument has not been found persuasive as the claimed invention has not been limited to those "high-fidelity enzymes" that would allow applicant to overcome these art-recognized issues. Therefore, with the claims fairly encompassing the use of any suitable polymerase, and the art recognizing that issues of fidelity do exist, the art cited is deemed appropriate and the rejection is maintained.

24. At page 11 of the response applicant presents argument as to how art-recognized difficulties can be overcome. This argument has not been found persuasive as applicant is arguing limitations not found in the claims.

25. At page 11, bridging to page 12 of the response, applicant agrees that DNA-dependent RNA polymerases may not incorporate fluorescently labeled NTPs during RNA synthesis, yet assert that they have not claimed such.

26. The above argument has not been found persuasive towards the withdrawal of the rejection for while applicant may not have explicitly claimed such limitations, these embodiments are fairly encompassed by the claims.

27. Agreement is reached with applicant in that the claimed invention is not a RT-PCR procedure in the traditional sense, however, the claimed method does fairly encompass producing cDNAs from a population of mRNAs where the RNA has secondary structures. And a noted in paragraph 17 above, such entities may be poorly represented in cDNA libraries, which are encompassed in claim 1, step (d), and claim 22, step (b) of the claimed invention.

28. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Conclusion

29. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

30. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
14 June 2004